PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Zuker *et al.*

Application No.: 09/361,652

Filed: July 27, 1999

For: **NUCLEIC ACIDS ENCODING A G-PROTEIN COUPLED RECEPTOR INVOLVED IN SENSORY TRANSDUCTION**

Examiner: Michael Brannock

Art Unit: 1646

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. CHARLES ZUKER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Charles Zuker, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I received my Ph.D. from Massachusetts Institute of Technology. I am currently a Professor and Investigator, Howard Hughes Medical Institute, Departments of Biology and Neurosciences, School of Medicine, University of California at San Diego. I have been in this position since 1986. See resume, Exhibit A.

4. The above-referenced patent application claims isolated nucleic acids encoding GPCR-B3, also known as T1R1, a taste bud specific G protein coupled receptor involved in taste transduction.

5. I am an inventor of the above-referenced patent application. I have read and am familiar with the contents of the patent application. In addition, I have read the Office Action, mailed August 12, 2001, received in the present case. It is my understanding that the Examiner believes that this invention is supported by neither a specific, substantial, and credible asserted utility nor a well established utility as required by the United States Patent Laws.

6. This declaration is provided to demonstrate that, at the time the application was filed, one of skill in the art would recognize the utility of the present invention and would appreciate its real world context.

7. The present application discloses that the claimed nucleic acid, a full length cDNA, encodes a G protein coupled receptor ("GPCR") that is specifically expressed in taste buds of the tongue, and provides data demonstrating that the claimed protein is a functional G-protein coupled receptor. The present invention is therefore useful, e.g., for screening for taste modulators of a taste bud cell specific GPCR, for the identification of GPCR-B3 taste ligands, and as a specific marker for specialized taste bud cells of the tongue.

8. As described in the present specification, full length cDNAs that encode a taste cell-specific nucleic acids were cloned. Sequence analysis of the GPCR-B3 clone showed that it had the structure of a G-protein coupled receptor, with an extracellular domain, seven transmembrane domains, and a cytoplasmic domain (*see, e.g.*, Example I, page 56-57). Subsequently, protein expression patterns were determined for GPCR-B3 using *in situ* analysis (*see, e.g.*, Example II, page 58, and Figure 3). Figure 3 shows that the claimed nucleic acids express proteins that are specifically expressed in taste buds of the tongue.

9. Furthermore, the specification provides experimental data demonstrating that GPCR-B3 is a functional G-protein coupled receptor. Figure 4 shows the structure of a chimeric protein, comprising an extracellular domain of a murine MGluR1 receptor fused to the seven transmembrane domains and cytoplasmic domains of GPCR-B3. This chimeric GPCR construct was transfected into HEK cells, which were then stimulated with glutamate, the MGluR1 ligand. The HEK cells demonstrated an increase in intracellular calcium in response to the ligand, indicating that the chimeric GPCR couples to a promiscuous G protein and triggers calcium responses that are detectable using the indicator fura-2. The presently claimed GPCR-B3 nucleic acids therefore encode a G protein coupled receptor that is specifically expressed in fungiform and foliate cells of the tongue, which are taste bud cells, as described in the specification.

10. It would be apparent to anyone of skill in the art that GPCR-B3 is an excellent target for candidate compounds that modulate taste transduction. This use is not merely a "starting point for further research and investigation," but a direct assay for taste ligands and modulators of taste signal transduction. Furthermore, the claimed nucleic acids are specifically expressed in a unique subset of tongue cells, and the encoded proteins localize to the taste pore- the subcellular location for taste receptors. As such, they have specific and substantial utility as markers for specialized taste cells of the tongue. Such markers are useful for the generation of taste topographic maps the

elucidate the relationship between taste bud cells of the tongue and taste sensory neurons leading to taste centers in the brain. Applicants have therefore provided a nucleic acid that encodes a protein with known signaling activity and specific expression in a specialized sub-set of cells.

11. In view of the foregoing, it is my scientific opinion that one of skill in the art, at the time the application was filed, would immediately recognize the real world utility of the nucleic acids of this invention. Therefore, this invention is supported by a specific, substantial, and credible utility.

Date: 9/10/02 By: _____

Charles Zuker, Ph.D.

CURRICULUM VITAE

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EDUCATION

INSTITUTION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Universidad Catolica de Valparaiso; Chile	B.Sc., Honors	1977	Biology
Massachusetts Inst. of Technology; Boston	Ph.D.	1983	Biology

RESEARCH AND/OR PROFESSIONAL EXPERIENCE

1993 - present	Professor and Investigator; Howard Hughes Medical Institute Departments of Biology and Neurosciences, School of Medicine University of California, San Diego
1989 - 1992	Associate Professor and Associate Investigator Howard Hughes Medical Institute, UCSD
1986 - 1989	Assistant Professor; Department of Biology, UCSD
1983 - 1986	Postdoctoral Fellow; Department of Biochemistry; University of California, Berkeley
1977 - 1983	Graduate Student; Department of Biology; Massachusetts Institute of Technology

Honors and Keynote Lectures (selected)

Whitaker Health Sciences Fund Fellow, Massachusetts Inst. of Technology, 1979-1980
Whitaker Health Sciences Fund Fellow, Massachusetts Inst. of Technology, 1981-1982
European Molecular Biology Organization Fellow, 1983
Jane Coffin Childs Memorial Fund for Medical Research Fellow, 1984-1986
McKnight Foundation Fund for Neuroscience Award, 1988-1991
Monsanto Speaker, St. Louis University, St Louis, MO, 1991
Broadhurst Foundation visiting lecturer, Cambridge, MA, 1991
Institute Speaker, Scripps Research Institute, La Jolla, CA, 1992
Keynote speaker, Stanford Neurosciences Program Retreat, Monterey, CA,1992
Pew Scholars Award, 1988-1992
Alfred P. Sloan Award in Neurosciences, 1988-1990
March of Dimes Basil O'Connor Award, 1989-1991
Merck Lecturer, UC Berkeley 1992
Institute speaker, Roche Institute of Molecular Biology, Nutley, NJ, 1993
Keynote Speaker, Pharmacological Sciences Program, Vanderbilt University, Nashville, TN, 1994
Keynote Speaker, Stanford Medical Scientist Training Program, Stanford University CA, 1994
Lecturer in the Life Sciences, Northwestern University Medical School, Chicago, IL 1994

Howard Hughes Medical Institute, Lecture series to Institute employees, Howard Hughes Medical Institute, Chevy Chase, MD, 1996
Keynote Speaker, FASEB Summer Conference on "The Biology and Chemistry of Vision", Keystone, CO, 1997
Keynote Speaker, U. Penn Graduate programs in Biochemistry, Molecular Biology and Pharmacology. Philadelphia, 1998
Cogan Award, Association for Research in Vision and Ophthalmology, 1998
University Lecturer, UT Southwestern Medical School, 1999
Alcon Award for outstanding contributions to vision research, 1999
American Academy of Arts and Sciences, 2000

Study Sections and Advisory Boards (selected):
Member, Scientific Advisory Board, Pew Latin American Scholars Program, 1990 - present
Mechanisms of Development, 1991-present
Neuron, 1995-present
Member, American Cancer Society Postdoctoral Research Selection Committee, 1995-1999
Member, Scientific Advisory Board, Schepens Research Institute, Harvard University, Cambridge, MA, 1995 - present
Member, Review Panel, Howard Hughes Medical Institute International Grants Program, 1996
Member, National Research Council/ National Academy of Sciences advisory committee for the US and HHMI program in Latin America, 1997-
National Advisory Committee of The Pew Scholars Program in the Biomedical Sciences, 1997-
Member, NIH Visual Sciences C study section, Bethesda, MD, 1997-2000
Member, NIDCD Strategic Planning committee 1999-
Damon Runyon-Walter Winchell Cancer Fund Scientific Advisory Committee, 1999-
Current Biology, 2000-
Steering Committee, Alliance for Cellular Signaling, 2000-
Advisory board, Pew program in Science and Society, 2001-
Advisory board, NIH-wide initiative on mouse mutagenesis, 2001-

Publications (selected):

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Feiler, R., W. Harris, K. Kirschfeld, C. Wehrhahn and C. Zuker (1988). Targeted misexpression of a *Drosophila* opsin gene leads to altered visual function. Nature *333:* 737-741.

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Schaeffer, E., D. Smith, G. Mardon, W. Quinn and C. Zuker (1989). Isolation and characterization of two new *Drosophila* protein kinase C genes, including one specifically expressed in photoreceptor cells. Cell *57:* 403-412.

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Stamnes, M.A., B.-H. Shieh, L. Chuman, G. L. Harris and C. S. Zuker (1991). The cyclophilin homolog ninaA is a tissue-specific integral membrane protein required for the proper synthesis of a subset of Drosophila rhodopsins. Cell. *65*: 219-227.

Smith, D. P., M. A. Stamnes and C. S. Zuker (1991). Signal transduction in the visual system of *Drosophila.* Ann. Rev. Cell Biol. *7*: 161-190.

Ranganathan, R., W. A. Harris and C. S. Zuker (1991). The genetics of phototransduction. Trends in Neurosci. *14*: 486-493.

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Ranganathan, R., G. L. Harris, C. F. Stevens, and C. S. Zuker. (1991). A Drosophila mutant defective in extracellular calcium-dependent photoreceptor deactivation and rapid desensitization. Nature *354*: 230-232.

Smith, D. P., R. Ranganathan, R. W. Hardy, J. Marx, T. Tsuchida, and C. S. Zuker (1991). Photoreceptor deactivation and retinal degeneration mediated by photoreceptor-specific protein kinase C. Science *254*: 1478-1484.

Cassill, J. A., M. Whitney, C. A. P. Joazeiro, A. Becker and C. S. Zuker (1991). Isolation of Drosophila genes encoding G protein-coupled receptor kinases. P. N. A. S., *USA 88*: 11067-11070.

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Feiler, R., R. Bjornson, K. Kirschfeld, D. Mismer,G. M. Rubin, D. P. Smith, M. Socolich and C. S. Zuker (1992). Ectopic expression of ultraviolet-rhodopsins in the blue photoreceptor cells of *Drosophila*: Visual physiology and photochemistry of transgenic animals. J. Neurosci., *12*:3862-3868.

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Dolph, P.J., H. Man-Son-Hing, S. Yarfitz, N.J. Colley, J. Running Deer, M. Spencer, J.B. Hurley, and C.S. Zuker (1994). An eye-specific Gb subunit essential for termination of the phototransduction cascade.; Nature; *370*: 59-61.

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Baker, E.B., N.J. Colley, and C.S. Zuker (1994). The cyclophilin homolog ninaA functions as a chaperone forming a stable complex *in vivo*, with its protein target, rhodopsin. EMBO, *13*: 101-110.

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Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, and Zuker CS. (2001). Mammalian sweet taste receptors. Cell, 106, 381-390

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